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(71) Applicant (for all designated States except BB, US): **TEVA PHARMACEUTICAL INDUSTRIES LTD.** [IL/IL]; 5 Basel Street, P.O. Box 1390, 49131 Petah Tikva (IL).

(71) Applicant (for BB only): **TEVA PHARMACEUTICALS USA, INC.** [US/US]; 1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **LERNER, Itzhak, E.** [IL/IL]; Wolfson 32, Petach Tikva (IL). **ROSENBERGER, Vered** [IL/IL]; Ms. Landau 3, Givalt Masuah, Jerusalem (IL). **FLASHNER-BARAK, Moshe** [IL/IL]; Hefetz Mordechai 15, Petach Tikva (IL). **DRABKIN,**

**Anna** [IL/IL]; Netafim 5/1, Tzur Hadassah (IL). **MOL-DAVSKI, Naomi** [IL/IL]; Mishol Hayaarah Ramot, Jerusalem (IL).

(74) Agents: **BRAINARD, Charles, R.** et al.; Kenyon & Kenyon, One Broadway, New York, NY 10004-1050 (US).

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(54) Title: **DRUG MICROPARTICLES**

(57) Abstract: Provided are microparticles of active pharmaceutical ingredients, drug delivery vehicles comprising same, and methods for making them.

WO 03/082247 A2

## **DRUG MICROPARTICLES**

### **FIELD OF THE INVENTION**

The present invention relates to microparticles of drugs, especially drugs that are  
5 poorly soluble in water, and to methods for making them.

### **RELATED APPLICATIONS**

The present Application claims the benefit of the March 26, 2002 filing date of  
United States Provisional Patent Application No. 60/367,957.

### **BACKGROUND OF THE INVENTION**

10 Many important drugs have poor oral bioavailability because they are poorly  
soluble in water. Many approaches have been suggested to overcome this problem.  
Although some approaches have been used, with limited commercial success, each  
approach has its own drawbacks and limitations.

In one approach, a water-soluble prodrug of a poorly water-soluble drug is made  
15 [1 – 4]. The prodrug approach is limited to those molecules that have functionality  
amenable to facile removal in the body to form the drug. Not all poorly water-soluble  
drugs are so endowed. Furthermore, the prodrug would likely be considered a new  
chemical entity and require separate approval from regulatory agencies, adding  
considerable time and cost to bringing the product to market.

20 The bioavailability of poorly water-soluble drugs has been improved by  
decreasing the particle size of the drug to increase the surface area. Milling [5 – 6], high  
pressure homogenization [7 – 8], spray drying [9], lyophilization of solutions in water –  
organic solvent mixtures [10], and lyophilization of solutions in organic solvents [11 – 12]  
have been tried. Size reduction is, in principal, generally applicable for improving  
25 bioavailability, but achieving size reduction by, for example, high energy milling,  
requires special equipment and is not always applicable. High pressure homogenization  
requires special equipment and requires organic solvents that can remain in the  
comminuted product. Spray drying also requires solvents and generally produces  
particles that are too large.

30 Lyophilization is usually limited to materials that are soluble in water in any  
event, although there have been some efforts at using organic solvents.

The solubility of poorly soluble antibiotics has been improved by complexation with polymers or cyclodextrins. Polymer complexes have been formed with PVP in organic solvent [13a], or with PVP in heated water [13]. Other drugs have been complexed with cyclodextrins and polymers [14 – 15].

5        The bioavailability of poorly soluble drugs has been improved by dispersing the drug in a soluble polymer, often with addition of surfactants [16 – 24].

Some combinations of techniques have shown added improvement. For example spraying and drying a dispersion of drug and polymer or cyclodextrin on pellets in a fluidized bed dried [25 – 26]. The combination of solid dispersion and lyophilization to  
10       improve solubility has been demonstrated [27], and the use of solid dispersions absorbed on a carrier having a large surface area has also been demonstrated [28].

Clearly, there is a need for a simpler and generally applicable means of making and delivering particles of drugs having a size below 10  $\mu\text{m}$  and especially below 1  $\mu\text{m}$ .

Many of the above-described techniques require forming particles by solvent  
15       removal which, in turn, entails concentration of a solution. During solution concentration, solute molecules, which in solution are statistically separated into individual molecules and small clusters or aggregates, are drawn together to form larger molecular aggregates. When the solute drug eventually precipitates, relatively larger crystals are formed.

20       Lyophilization (freeze drying) has the advantage of allowing the solvent to be removed whilst keeping the solute relatively immobile, thereby suppressing enlargement of clusters or aggregates. When the solvent is removed, the formed crystals are smaller or the material is amorphous, reflecting the separation of the molecules in the frozen solution state. Molecular separation can be improved and aggregate formation still  
25       further suppressed by lyophilizing a more dilute solution, although one pays a hefty price in energy requirements for removing more solvent. Lyophilization is usually a very slow, energy intensive process and usually requires high vacuum equipment. Furthermore, there is a tendency for the crystals formed to aggregate in the free state, undoing the job that the freeze drying did. This tendency can sometimes be overcome with additives, but  
30       ~~these must be compatible with the entire system.~~

Amorphous or nanoparticulate materials tend to show poor bulk flow properties as powders, requiring formulation work to be able to fill them into capsules. While these problems are not insurmountable, they add further limitations in the usefulness of the system. Many of the existing limitations are overcome by the present invention.

5

### SUMMARY OF THE INVENTION

The present invention relates to a drug delivery vehicle including a pharmaceutical carrier particle, especially a pharmaceutical carrier particle that is a sugar particle, a starch particle, a lactose particle, or a particle of microcrystalline cellulose, bearing microparticles of a drug, especially a drug having poor solubility in water, wherein the microparticles of the drug are deposited on the pharmaceutical carrier particle from a solid solution of the drug in a sublimable carrier such as menthol, thymol, camphor, t-butanol, trichloro-*t*-butanol, imidazole, coumarin, acetic acid (glacial), dimethylsulfone, urea, vanillin, camphene, salicylamide, and 2-aminopyridine. The drug delivery vehicle of the present invention is useful for delivering a drug, especially a drug that has poor solubility in water, to a mammal, especially a human, in need of treatment with that drug.

In another aspect, the present invention relates to a method of making a microparticle including the steps of forming a solid solution of the drug in a sublimable carrier and removing the sublimable carrier from the solid solution by, for example, sublimation. Sublimation can be accomplished in a fluidized bed apparatus.

In another aspect, the present invention relates to a method of making a drug delivery vehicle including the steps of forming a solid solution of the drug and a sublimable carrier on the surface of a pharmaceutical carrier particle, especially a pharmaceutical carrier particle that is a sugar particle, a starch particle, a lactose particle, or a particle of microcrystalline cellulose, and removing the sublimable carrier from the solid solution, for example by sublimation, to deposit microparticles of the drug on the pharmaceutical carrier particle. The solid solution can be formed on the carrier particle by, for example, combining drug, sublimable carrier, and a solvent (for example ethanol), applying the combination to the carrier particle, and removing the solvent. The solid solution can also be formed by applying a combination of drug and molten sublimable carrier to the particle and allowing the combination to cool to form the solid solution on the carrier particle.

In yet another aspect, the present invention relates to pharmaceutical compositions that include microparticles of the present invention, which microparticles can be born by a drug delivery vehicle of the present invention.

### **DETAILED DESCRIPTION OF THE INVENTION**

5       The present invention provides microparticles of a pharmacologically active substance, i.e. a drug, and a method for making them. The invention also provides a drug delivery vehicle for administering a pharmacologically active substance, and methods for making it, wherein the delivery vehicle includes at least one pharmaceutical carrier particle bearing microparticles of the drug, which microparticles are made according to  
10       the present invention.

      Microparticles of the present invention are formed as described hereinbelow and generally have mean dimensions on the order of about 100 nm, up to about 10  $\mu$ m. Microparticles according to the present invention can have a regular shape, e.g. essentially spherical, or they can have an irregular shape. The material of which  
15       microparticles are comprised can be crystalline or it can be at least partly amorphous. Preferably the material is at least partly amorphous.

      As used herein in connection with a measured quantity, the term about refers to the normal variation in that measured quantity that would be expected by the skilled artisan making the measurement and exercising a level of care commensurate with the  
20       objective of the measurement and the precision of the measuring equipment used.

      Any pharmacologically active substance (drug) can be used in the practice of the present invention. However, drugs having poor water solubility (poorly water soluble drugs), and hence relatively lower bioavailability, are preferred and the advantages of the present invention are more fully realized with poorly water-soluble drugs. For purposes  
25       of the present invention, a drug is considered to be poorly water soluble if it has a solubility of less than about 20 mg/ per milliliter of water. Examples of drugs having poor water solubility include fenofibrate, itraconazole, bromocriptine, carbamazepine, diazepam, paclitaxel, etoposide, camptothecin, danazole, progesterone, nitrofurantoin, estradiol, estrone, oxfendazole, proquazone, ketoprofen, nifedipine, verapamil, and  
30       glyburide, to mention just a few. The skilled artisan knows other drugs having poor water solubility.

Pharmaceutical carrier particles useful for making the delivery vehicle of the present invention are made of comestible substances and are well known in the art. Examples of useful pharmaceutical carrier particles include particles, that can be non-pariel pellets, typically between about 0.1 mm. and about 2 mm. in diameter, and made of, for example, starch, particles of microcrystalline cellulose, lactose particles or, particularly, sugar particles. Suitable sugar particles (pellets, e.g. non-pariel 103, Nu-core, Nu-pariel) are commercially available in sizes from 35 to 40 mesh to 18 to 14 mesh. Particles of microcrystalline cellulose are preferred pharmaceutical carrier particles. The skilled artisan knows other pellets or spheres useful as pharmaceutical carrier particles.

The microparticles of the drug or pharmacologically active substance of the present invention are obtained by removing a sublimable carrier from a solid solution of the drug in the sublimable carrier. The drug or pharamaceutically active substance can be present with the sublimable carrier in the solid solution as discrete molecules, or it can be present in aggregates of a few hundred, a few thousand, or more molecules. The drug need only be dispersed on a sufficiently small scale so that sufficiently small, discrete microparticles are ultimately obtained. Preferably, the drug or pharmagolocigally active substance in the solid solution is dissolved in the sublimable carrier.

Sublimable carriers useful in the practice of the present invention form solid solutions with the drug at an easily accessible temperature and can be removed from the solid solution without heating the solid solution to a temperature above the melting point of the solid solution, for example by sublimation. Sublimable carriers have a measurable vapor pressure below their melting point. Preferred sublimable carriers have a vapor pressure of at least about 10 Pascal, more preferably at least about 50 Pascal at about 10° or more below their normal melting points. Preferably, the sublimable carrier has a melting point between about -10° C and about 200°C, more preferably between about 20° C and about 60° C, most preferably between about 40°C and about 50° C. Preferably, the sublimable carrier is a substance that is classified by the United States Food and Drug Administration as generally recognized as safe (i.e., GRAS). Examples of suitable sublimable carriers include menthol, thymol, camphor, t-butanol, trichloro-*t*-butanol, imidazole, coumarin, acetic acid (glacial), dimethylsulfone, urea, vanillin, camphene, ~~salicylamide, and 2-quinopridine. Menthol is a particularly preferred sublimable~~ carrier.

The solid solutions of the present invention can exist as a true homogeneous crystalline phase of the interstitial or substitutional type, composed of distinct chemical species occupying the lattice points at random, or they can be a dispersion of discrete molecules or aggregates of molecules in the sublimable carrier.

5       The solid solutions can be made by combining a drug with molten sublimable carrier, then cooling the combination to below the melting point of the solid solution. The solid solutions can also be formed by combining drug and sublimable carrier in an organic solvent and evaporating the organic solvent to obtain a solid solution of drug in sublimable carrier. Ethanol is an example of a preferred organic solvent that can be used  
10   in the practice of the present invention.

The solid solution can also include a compound or polymer that forms a dispersion with the drug.

In a preferred embodiment, the solid solution is formed on the surface of at least one pharmaceutical carrier particle and preferably a plurality of pharmaceutical carrier  
15   particles. For example, a molten combination of drug and carrier can be applied to the surface of a pharmaceutical carrier particle where it is allowed to cool to form the solid solution on the surface of the pharmaceutical carrier particle. A solid solution can also be formed at the surface of a pharmaceutical carrier particle by applying a combination of solvent, drug, and sublimable carrier to at least one, and preferably a plurality of,  
20   pharmaceutical carrier particle(s) and evaporating the organic solvent to obtain the solid solution on the surface of the pharmaceutical carrier particle.

Application to the pharmaceutical carrier particles can be by any particle coating technique known in the art, for example using fluidized bed equipment or a spray coater. When used, organic solvent is removed after application by exposing the coated carrier  
25   particles to vacuum or a stream of heated or non-heated air using particle handling equipment well known in the art.

When no solvent is used, application is at a temperature above the melting point of the sublimable carrier. When drug and sublimable carrier are combined with solvent, application is at a temperature such that drug and sublimable carrier remain in solution in  
30   the solvent.

The microparticles of the present invention are formed by removal of sublimable carrier from a solid solution, made as described above, at a temperature below the melting point of the solid solution. The solid solution must be kept at a temperature below its melting point to preserve the solid solution during the process of removing the sublimable carrier. The sublimable carrier can be removed from the solid solution by, for example, treating the solid solution, deposited on a pharmaceutical carrier particle where applicable, in a stream of air, preferably heated air, in, for example, a fluidized bed drier.

In those embodiments in which the solid solution is coated on the surface of a pharmaceutical carrier particle, the sublimable carrier can be removed by exposing the coated particles to heat, vacuum, heat and vacuum, or to a stream of heated or non-heated air, for example in a fluidized bed dryer. Exposing coated pharmaceutical carrier particles to a stream of air (heated or not) in a fluidized bed dryer is a preferred means of removing sublimable carrier from solid solution coated on pharmaceutical carrier particles in order to form the microparticles of the present invention on the surface of the carrier particles.

Removal of sublimable carrier from the solid solution, whether coated on a pharmaceutical carrier particle or not, results in formation of the microparticles of the present invention.

In another embodiment of the present invention, the microparticles of drug or the pharmaceutical carrier particles bearing microparticles of a drug are formulated into pharmaceutical compositions that can be made into dosage forms, in particular oral solid dosage forms such as capsules and compressed tablets, as are well known in the art.

Compressed tablets are formulated from pharmaceutical compositions containing the microparticles of the pharmacologically active substance or drug, or using pharmaceutical carrier particles bearing such microparticles, and pharmacologically inert (pharmaceutically acceptable) additives or excipients.

For making a tablet, it will typically be desirable to include one or more benign pharmaceutical excipients in the pharmaceutical composition. The pharmaceutical composition of the present invention may contain one or more diluents added to make the tablet larger and, hence, easier for the patient and caregiver to handle. Common diluents are microcrystalline cellulose (e.g. Avicel®), microfine cellulose, lactose, starch, pregelatinized starch, calcium carbonate, calcium sulfate, sugar, dextrates, dextrin,



dextrose, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, polymethacrylates (e.g. Eudragit®), potassium chloride, powdered cellulose, sodium chloride, sorbitol and talc.

Binders also may be included in tablet formulations to help hold the tablet together after compression. Some typical binders are acacia, alginic acid, carbomer (e.g. carbopol), carboxymethylcellulose sodium, dextrin, ethyl cellulose, gelatin, guar gum, hydrogenated vegetable oil, hydroxyethyl cellulose, hydroxypropyl cellulose (e.g. Klucel®), hydroxypropyl methyl cellulose (e.g. Methocel®), liquid glucose, magnesium aluminum silicate, maltodextrin, methylcellulose, polymethacrylates, povidone (e.g. Kollidon®, Plasdone®), pregelatinized starch, sodium alginate and starch.

The tablet may further include a disintegrant to accelerate disintegration of the tablet in the patient's stomach. Disintegrants include alginic acid, carboxymethyl cellulose calcium, carboxymethylcellulose sodium, colloidal silicon dioxide, croscarmellose sodium (e.g. Ac-Di-Sol®, Primellose®), crospovidone (e.g. Kollidon®, Polyplasdone®), guar gum, magnesium aluminum silicate, methyl cellulose, microcrystalline cellulose, polacrilin potassium, powdered cellulose, pregelatinized starch, sodium alginate, sodium starch glycolate (e.g. Explotab®) and starch.

A pharmaceutical composition for making compressed tablets may further include glidants, lubricants, flavorings, colorants and other commonly used excipients.

Pharmaceutical carrier particles bearing microparticles of a drug made in accordance with the present invention have excellent bulk flow properties and can be used directly, alone or in combination with carrier particles that do not carry a drug, to make capsule dosage forms. If necessary, diluents such as lactose, mannitol, calcium carbonate, and magnesium carbonate, to mention just a few, can be formulated with the microparticle-bearing pharmaceutical carrier particles when making capsules

Liquid oral pharmaceutical compositions of the present invention comprise microparticles or microparticle-bearing pharmaceutical carrier particles and a liquid carrier such as water, vegetable oil, alcohol, polyethylene glycol, propylene glycol or glycerin, most preferably water.

~~Liquid oral pharmaceutical compositions may contain emulsifying agents to~~  
disperse uniformly throughout the composition the active ingredient, drug delivery

vehicle, or excipient having low solubility in the liquid carrier. Emulsifying agents that may be useful in liquid compositions of the present invention include, for example, gelatin, egg yolk, casein, cholesterol, acacia, tragacanth, chondrus, pectin, methyl cellulose, carbomer, cetostearyl alcohol and cetyl alcohol.

5           Liquid oral pharmaceutical compositions of the present invention may also contain a viscosity enhancing agent to improve the mouth-feel of the product and/or coat the lining of the gastrointestinal tract. Such agents include acacia, alginic acid bentonite, carbomer, carboxymethylcellulose calcium or sodium, cetostearyl alcohol, methyl cellulose, ethylcellulose, gelatin guar gum, hydroxyethyl cellulose, hydroxypropyl  
10 cellulose, hydroxypropyl methyl cellulose, maltodextrin, polyvinyl alcohol, povidone, propylene carbonate, propylene glycol alginate, sodium alginate, sodium starch glycolate, starch tragacanth and xanthan gum.

          The liquid oral pharmaceutical composition also may contain sweetening agents, such as sorbitol, saccharin, sodium saccharin, sucrose, aspartame, fructose, mannitol and  
15 invert sugar; preservatives and chelating agents such as alcohol, sodium benzoate, butylated hydroxy toluene, butylated hydroxyanisole and ethylenediamine tetraacetic acid; and buffers such as gluconic acid, lactic acid, citric acid or acetic acid, sodium gluconate, sodium lactate, sodium citrate or sodium acetate.

          The present invention is further illustrated with the following non-limiting  
20 examples.

#### Example 1 – Solubility of selected drugs in menthol

          The following general procedure was repeated with several drugs with menthol carrier.

          Menthol (10 grams) was melted on a stirring hot plate with magnetic stirring, then  
25 heated to the desired temperature indicated in Table 1. The desired drug was added in small increments (0.1 grams) and stirred to obtain a clear solution. The desired drug was added in increments until no more drug dissolved in the menthol. The weight of material added to the menthol melt that still gave a clear solution was taken as the solubility of the active drug at the indicated temperature. The results are given in Table 1.

30 ~~Table 1. Solubility of selected active drug substances in menthol.~~

<u>Active drug substance</u>	<u>temperature (°C)</u>	<u>Solubility</u> <u>(%w/w)</u>
Azithromycin	63	40.0
Cyclosporin	55	39.2
Diazepam	43	5.7
Fenofibrate	60	37.5
Itraconazole	61	1.0
Oxybutynin	60	9.1
Risperidone	70	8.3
Salicylic acid	43	16.0
Simvastatin	63	30.0

**Example 2 – Improvement of the dissolution of fenofibrate by “menthol micronization”**

Menthol (50 grams) was heated in a jacketed reactor to 60°C. After melting, the melt was stirred at 100 rpm. Fenofibrate (25 grams) was added and the mixture stirred at 100 rpm and 60°C until full dissolution was achieved. Microcrystalline cellulose (Avicel ph 102, 55 grams) was added to the melt and the mixture was stirred for 30 minutes. The heat source was then removed and the mass allowed to cool to room temperature with the stirring continued at 100 rpm for a further 30 minutes.

The obtained mass was milled through a 6.35 mm screen in a Quadro Comil mill at 1300 rpm. The milled product was allowed to cool to 25°C and milled again through 1.4 mm screen to obtain a powder in which the fenofibrate is dissolved in menthol and coated on the microcrystalline cellulose.

The powder was transferred to a fluid bed dryer (Aeromatic model STREA1) where the menthol was removed by drying for three hours at 30 – 32°C with the fan at 7-8 Nm<sup>3</sup>/hr. A powder, 62 grams, was obtained. This powder was an essentially “micronized” fenofibrate deposited on microcrystalline cellulose.

A sample of this powder containing 100 mg of the fenofibrate was tested for dissolution in a USP Apparatus II dissolution tester in 900 ml 0.5% sodium lauryl sulfate

(SLS) in water at 37°C and 100 rpm. The fenofibrate in the dissolution medium was determined by HPLC on an Hypersil® ODS column with UV detection at 286 nm. The results are shown in Table 2. Fenofibrate “micronized” by the menthol method gave 100% dissolution in two hours. An equivalent simple combination of fenofibrate (control, not deposited from menthol) with microcrystalline cellulose gave 40.2% dissolution in 3 hours, while a mechanically micronized fenofibrate raw material mixed with microcrystalline cellulose gave 72.1% dissolution in 3 hours.

Table 2. Dissolution of menthol treated fenofibrate

time (minutes)	% dissolved
15	44.0+/- 1.3
30	73.6 +/- 2.9
60	82.3+/- 0.6
90	93.1+/-4.2
120	102.7+/-0.2
180	104.9+/-0.8

10 Example 3 - Improvement of the dissolution of oxybutynin chloride by “menthol micronization”

Menthol (80 grams) was melted and oxybutynin chloride (8 grams) and microcrystalline cellulose (89.5 grams) were added and treated as in Example 2 to give a powder of “micronized” oxybutynin chloride on microcrystalline cellulose.

15 The dissolution of oxybutynin chloride from this powder ( a sample of powder containing 100 mg of the active drug) was tested in a USP apparatus II dissolution tester in 100 ml of 50 mM phosphate buffer pH = 6.8 at 37°C and 50 rpm. The oxybutynin content of the dissolution sample was measured by spectrophotometer at 225 nm. The results are given in Table 3. The dissolution reached 79.2% at three hours. An equivalent  
20 simple combination of the oxybutynin chloride raw material with microcrystalline cellulose that was not treated with the “menthol micronization” method gave only 22.1% dissolution in three hours.

Table 3. Dissolution of menthol treated oxybutynin

time (minutes)	% dissolved
30	21.5 +/- 0.4
90	59.7 +/- 1.2
180	79.2 +/- 1.0

Example 4 – Improvement of the dissolution of risperidone by “menthol micronization”

Menthol (50 grams) was melted and risperidone (4.5 grams) and microcrystalline cellulose (62.5 grams) were added and treated according to the procedure in Example 2. A sample of the resulting powder (containing 50 mg of risperidone ) was tested in a USP apparatus II dissolution tester using 900 ml of water at 37°C and 100 rpm. The concentration of risperidone in the dissolution samples was measured using a spectrophotometer at 240 nm.

The results of the dissolution of the “menthol micronized” powder and of the control simple combination of risperidone and microcrystalline cellulose (not treated with menthol) are shown in Table 4. The menthol deposited risperidone gave 100% dissolution in 30 minutes, whereas the control mixture gave 31.9% in thirty minutes and 63.7% in three hours.

Table 4. Dissolution of menthol treated risperidone vs. control

time (minutes)	% dissolved test	% dissolved control
15	69.3 +/- 0.5	17.5 +/- 2.6
30	99.9 +/- 1.0	31.9 +/- 3.5
60	102.3 +/- 0.8	41.7 +/- 5.6
90	102.8 +/- 1.2	48.2 +/- 8.3
120		53.2 +/- 11.1
180		63.7 +/- 8.3

Example 5 - Improvement of the dissolution of cyclosporin by "menthol micronization"

Menthol (80 grams) was melted and cyclosporin (20 grams) and microcrystalline cellulose (100 grams) were added and treated as in Example 2. A sample of this powder (containing 10 mg of "menthol micronized" cyclosporin) was tested for dissolution in 900 ml water in a USP apparatus II dissolution unit at 37°C and 100 rpm. The cyclosporin content of the dissolution samples was determined spectrophotometrically at 215 nm. The dissolution of the menthol deposited material and of a control mixture of cyclosporin and microcrystalline cellulose (not deposited from menthol) are presented in Table 5. The cyclosporin dissolution from the powder having cyclosporin deposited from menthol was about twice that of the control (simple combination), and the maximum dissolution was achieved in shorter time.

Table 5. Dissolution of menthol treated cyclosporin vs. control

time (minutes)	% dissolved test	% dissolved control
30	9.2 +/- 0.3	0.1 +/- 0.0
60	11.9 +/- 0.3	1.3 +/- 0.5
90	13.1 +/- 0.5	3.1 +/- 0.2
120	13.3 +/- 0.3	5.1 +/- 0.2
180	14.3 +/- 0.8	7.1 +/- 0.3

Example 6 (comparative)- Attempted improvement in itraconazole dissolution by "menthol micronization"

Menthol (92 grams) was melted as in Example 2. Itraconazole (3.6 grams) was added and mixed well in the melt. A solution was not formed because itraconazole has a solubility of only 1% in menthol at 60°C (see Table 1). To the suspension of itraconazole in menthol was added microcrystalline cellulose (90 grams) and the mixture treated as in Example 2. The dissolution of the itraconazole was measured from a powder sample containing 100 mg of the drug in 900 ml of 0.1N HCl in a USP apparatus II dissolution tester at 37°C and 100 rpm. The dissolved itraconazole was measured spectrophotometrically at 251 nm. The results of the dissolution are shown in Table 6. The dissolution was about 8% at 30 minutes and the same at three hours. A control

simple mixture of itraconazole and microcrystalline cellulose (not deposited from menthol) gave essentially the same results (7.8% in three hours).

Table 6. Dissolution of menthol treated itraconazole

time (minutes)	% dissolved
30	8.8 +/- 0.4
90	8.0 +/- 0.6
180	8.1 +/- 0.1

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### REFERENCES

- (1) Nielsen, L.S. *Improved peroral bioavailability of mebendazole in rabbits by administration of various N-alkoxycarbonyl derivatives of mebendazole*, Int. J. Pharm. **104**, 175-179 (1994)
- 10 (2) Chan, O. H. et. al. *Evaluation of a targeted prodrug strategy to enhance oral absorption of poorly water soluble compounds*, Pharm. Res. **15**, 1012-1018 (1998)
- 15 (3) Fleisher, D. et. al. *Improved oral drug delivery: Solubility limitations overcome by the use of prodrugs*, Adv. Drug Deliv. Rev. **19**, 115-130 (1996)
- (4) Abang, A. M. *The clinical pharmacology of topoisomerase I inhibitors*, Semin. Hematol. **35 Suppl 4**, 13-21 (1998)
- 20 (5) Merisko-Liversidge, E., *Formulation and antitumor activity evaluation of nanocrystalline suspensions of poorly soluble anticancer drugs*, Pharm. Res. **13**, 272-278 (1996);
- 25 (6) Liversidge, G. G., *Particle size reduction for improvement of oral bioavailability of hydrophobic drugs: I. Absolute oral bioavailability of nanocrystalline danazol in beagle dogs*, Int. J. Pharm., **125**, 91-97 (1995)
- (7) Muller, R. H., et. al. *Nanosuspensions for the formulation of poorly soluble drugs. I. Preparation by a size reduction technique*, Int. J. Pharm. **160**, 229-237 (1998)
- 30 (8) Muller, R. H. et. al. , *Increase of solubility of poorly soluble drugs by transfer to DissoCubes™ using high pressure homogenization*, Proc. Control. Release Soc. **1999**, 112-113,
- 35 (9) US patent 6,346,533 to Cha et. al

- (10) Morita, T. et. al. *Formation and isolation of spherical fine protein microparticles through lyophilization of protein-poly(ethylene glycol) aqueous mixtures*, Pharm. Res. **17**, 1367- 1373 (2000)
- 5 (11) Tesconi, M. S. , *Freeze drying above room temperature*, J. Pharm. Sci. **88**, 501-506 (1999)
- (12) Ni, N. et. al. *Use of pure butanol as a solvent for freeze drying: a case study*, Int. J. Pharm. **226**, 39-46 (2001)
- 10 (13a) US patent 3,089,818 assigned to Baxter laboratories
- (13) US Patent 4,900,775 to Smith et. al
- 15 (14) Wenz, G. *An overview of host-guest chemistry and its application to nonsteroidal anti-inflammatory drugs*, Clin. Drug Invest. **19 (suppl 2)**, 21-25 (2000)
- (15) Cappello, B. , *Solubilization of tropicamide by hydroxypropyl- $\beta$ -cyclodextrin and water soluble polymers: In vitro/in vivo studies*, Int. J. Pharm. **213**, 75-81 (2001)
- 20 (16) Sekiguchi et. al. Chem Pharm. Bull. **9**, 866-872 (1961)
- (17) Chiou et. al. J. Pharm. Sci. **60**, 1281-1302 (1971)
- 25 (18) Fernandez, M. et. al. , *Characterization of solid dispersions of piroxicam/polyethylene glycol 4000*, Int. J. Pharm. **84**, 197-202 (1992)
- (19) Margarit, M. V. et. al. , *Physical characteristics and dissolution kinetics of solid dispersions of ketoprofen and polyethylene glycol 6000*, Int. J. Pharm. **108**, 101-108
- 30 (1994)
- (20) Sheen, P.C. et. al., *Formulation of poorly water-soluble drug in solid dispersions to improve bioavailability*, Int. J. Pharm. **118**, 221-227 (1995)
- 35 (21) Kai, T. et. al., *Oral absorption of poorly soluble drug using solid dispersion technique*, Chem. Pharm. Bull. **44**, 568-571 (1996)
- (22) Serajuddin, A. T. M., *Solid dispersions of poorly water-soluble drugs: Early promises, subsequent problems, and recent breakthroughs*, J. Pharm. Sci., **88**, 1058-1066
- 40 (1999)
- (23) Lee, E. J. et. al. , *Bioavailability of cyclosporin A dispersed in sodium lauryl sulfate-dextrin based solid microspheres*, Int. J. Pharm., **218**, 125-131 (2001)
- 45 (24) Kapsi, S. G. et. al. *Processing factors in development of solid solution formulation of itraconazole for enhancement of drug dissolution and bioavailability*, Int. J. Pharm., **229**, ~~193-203 (2001)~~
- 50 (25) Ho, H. O., *The preparation and characterization of solid dispersions on pellets using a fluidized bed system*, Int. J. Pharm. **139**, 223-239 (1996)



(26) US Patent 6,027,747 to Terracol et. al.

(27) Betageri, G. V. et. al. *Enhancement of dissolution of glyburide by solid dispersion and lyophilization techniques*, Int. J. Pharm. **126**, 155-160 (1995)

(28) Gupta, M. K. et. al. *Enhanced drug dissolution and bulk properties of solid dispersions granulated with a surface adsorbent*, Pharm. Dev. Technol. **6**, 563-572 (2001)

What is claimed is;

1. A drug delivery vehicle comprising a pharmaceutical carrier particle bearing microparticles of a drug deposited on the pharmaceutical carrier particle from a solid solution of the drug in a sublimable carrier.
2. The drug delivery vehicle of claim 1 wherein the drug is a poorly water soluble drug.
3. The drug delivery vehicle of claim 2 wherein the poorly water soluble drug is selected from the group consisting of: fenofibrate, itraconazole, bromocriptine, carbamazepine, diazepam, paclitaxel, etoposide, camptothecin, danazole, progesterone, nitrofurantoin, estradiol, estrone, oxfendazole, proquazone, ketoprofen, nifedipine, verapamil, and glyburide.
4. The drug delivery vehicle of claim 1 wherein the sublimable carrier comprises one or more members selected from the group consisting of menthol, thymol, camphor, t-butanol, trichloro-*t*-butanol, imidazole, coumarin, acetic acid (glacial), dimethylsulfone, urea, vanillin, camphene, salicylamide, and 2-aminopyridine.
5. The drug delivery vehicle of claim 4 wherein the sublimable carrier is menthol.
6. The drug delivery vehicle of claim 1 wherein the pharmaceutical carrier particle comprises at least one pharmaceutical particle selected from starch particles, microcrystalline starch particles, microcrystalline cellulose particles, lactose particles, and sugar particles.
7. The drug delivery vehicle of claim 6 wherein the pharmaceutical carrier particle comprises particles of microcrystalline cellulose.
8. The method of claim 6 wherein the solid solution is formed by combining the drug and sublimable carrier with an organic solvent and thereafter evaporating the organic solvent to obtain the solid solution.

9. A method of making a drug delivery vehicle comprising the steps of:
- a) forming a solid solution of the drug and a sublimable carrier on the surface of a pharmaceutical carrier particle, and
  - b) subliming the sublimable carrier from the solid solution to deposit microparticles of the drug on the surface of the pharmaceutical carrier particle to obtain the drug delivery vehicle.
10. The method of claim 9 wherein the solid solution is formed by combining the drug with molten sublimable carrier, applying the combination to at least one pharmaceutical carrier particle, and thereafter allowing the combination to solidify to obtain the solid solution on the surface of the pharmaceutical carrier particle.
11. The method of claim 9 wherein the solid solution is formed by combining the drug and the sublimable carrier with an organic solvent, applying the combination to at least one pharmaceutical carrier particle, and evaporating the organic solvent to obtain the solid solution on the surface of the at least one pharmaceutical carrier particle.
12. The method of claim 11 wherein the solvent is ethanol.
13. The method of claim 9 wherein the drug is selected from the group consisting of fenofibrate, itraconazole, bromocriptine, carbamazepine, diazepam, paclitaxel, etoposide, camptothecin, danazole, progesterone, nitrofurantoin, estradiol, estrone, oxfendazole, proquazone, ketoprofen, nifedipine, verapamil, and glyburide.
14. The method of claim 9 wherein the sublimable carrier is selected from the group consisting of menthol, thymol, camphor, t-butanol, trichloro-*t*-butanol, imidazole, coumarin, acetic acid (glacial), dimethylsulfone, urea, vanillin, camphene, salicylamide, and 2-aminopyridine.
15. The method of claim 9 wherein the pharmaceutical carrier particle is selected from the group consisting of starch particles, sugar particles, lactose particles, particles of microcrystalline cellulose, and mixtures of any of these.

16. The method of claim 9 wherein the sublimable carrier is sublimed from the solid solution by treating the pharmaceutical carrier particles in a fluidized bed drier at a temperature below the melting point of the solid solution.

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17. A pharmaceutical composition comprising a plurality of microparticles of a drug and at least one pharmaceutically acceptable excipient, wherein the microparticles are formed by removing sublimable carrier from a solid solution of the drug in the sublimable carrier..

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18. The pharmaceutical composition of claim 17 wherein the solid solution is formed on the surface of a plurality of pharmaceutical carrier particle.

19. The pharmaceutical composition of claim 17 wherein the sublimable carrier is removed from the solid solution that is on the surfaces of the plurality of pharmaceutical carrier particles, whereby the plurality of microparticles are born by the plurality of pharmaceutical carrier particles.

20. An oral solid dosage form comprising a pharmaceutical composition according to claim 16.

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- (71) Applicant (for all designated States except BB, US): **TEVA PHARMACEUTICAL INDUSTRIES LTD.** [IL/IL]; 5 Basel Street, P.O. Box 1390, 49131 Petah Tikva (IL).
- (71) Applicant (for BB only): **TEVA PHARMACEUTICALS USA, INC.** [US/US]; 1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **LERNER, Itzhak**, E. [IL/IL]; Wolfson 32, Petach Tikva (IL). **ROSENBERGER, Vered** [IL/IL]; Ms. Landau 3, Givalt Masuah, Jerusalem (IL). **FLASHNER-BARAK, Moshe** [IL/IL]; Hefetz-Mordechai 15, Petach Tikva (IL). **DRABKIN, Anna** [IL/IL]; Netafim 5/1, Tzur Hadassah (IL). **MOLDAVSKI, Naomi** [IL/IL]; Mishol Hayaarah Ramot, Jerusalem (IL).
- (74) Agents: **BRAINARD, Charles, R.** et al.; Kenyon & Kenyon, One Broadway, New York, NY 10004-1050 (US).
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(54) Title: DRUG MICROPARTICLES

(57) Abstract: Provided are microparticles of active pharmaceutical ingredients, drug delivery vehicles comprising same, and methods for making them.

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# INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 A61K9/14

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## B. FIELDS SEARCHED

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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WPI Data, PAJ, EPO-Internal, EMBASE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 08987 A (KRKA TOVARNA ZDRAVIL) 6 April 1995 (1995-04-06)	1-7, 17-20
Y	page 7; example 1 page 8; example 4B page 9; example 8 figure 3	8-16
Y	WO 91 04733 A (THE MENTHOLATUM COMPANY LIMITED) 18 April 1991 (1991-04-18) claim 1	8-16
A	WO 01 89485 A (HANMI PHARM. CO., LTD.) 29 November 2001 (2001-11-29) page 7 -page 8; example 1	1-20
A	FR 2 199 973 A (BOEHRINGER MANNHEIM G.M.B.H.) 19 April 1974 (1974-04-19) page 7, line 8 - line 15	1-20
	--- -/--	



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Patent family members are listed in annex.

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European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Benz, K

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>WO 93 18757 A (PFIZER INC.)  30 September 1993 (1993-09-30)  page 4, line 20 - line 23  page 11 -page 12; example 1  -----</p>	1-20

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat

pplication No

PCT/US 03/09327

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9508987	A	06-04-1995	SI 9300504 A	30-04-1995
			CZ 9600900 A3	11-09-1996
			EP 0721329 A1	17-07-1996
			FI 961394 A	27-03-1996
			HR 940611 A1	31-10-1996
			HU 75643 A2	28-05-1997
			NO 961242 A	09-05-1996
			PL 313712 A1	22-07-1996
			WO 9508987 A1	06-04-1995
			SK 37996 A3	05-02-1997
WO 9104733	A	18-04-1991	AU 6504190 A	28-04-1991
			CA 2067131 A1	27-03-1991
			EP 0493496 A1	08-07-1992
			WO 9104733 A1	18-04-1991
			GB 2239600 A	10-07-1991
			JP 5502440 T	28-04-1993
WO 0189485	A	29-11-2001	CN 1380829 T	20-11-2002
			EP 1283703 A1	19-02-2003
			WO 0189485 A1	29-11-2001
			US 2003185886 A1	02-10-2003
			US 2002001617 A1	03-01-2002
FR 2199973	A	19-04-1974	DE 2246013 A1	28-03-1974
			AT 324568 B	10-09-1975
			CH 579394 A5	15-09-1976
			FR 2199973 A1	19-04-1974
			GB 1381588 A	22-01-1975
			IT 998618 B	20-02-1976
			JP 49069819 A	05-07-1974
			SE 395366 B	15-08-1977
			US 3885026 A	20-05-1975
WO 9318757	A	30-09-1993	AT 140625 T	15-08-1996
			AU 3057592 A	21-10-1993
			BR 9207104 A	05-12-1995
			CA 2131089 A1	18-09-1993
			CZ 9402258 A3	18-01-1995
			DE 69212503 D1	29-08-1996
			DE 69212503 T2	12-12-1996
			DK 630237 T3	26-08-1996
			EP 0630237 A1	28-12-1994
			ES 2089581 T3	01-10-1996
			FI 944309 A	16-09-1994
			GR 3020666 T3	31-10-1996
			HU 75616 A2	28-05-1997
			IL 105016 A	12-09-1996
			JP 2559206 B2	04-12-1996
			JP 7501829 T	23-02-1995
			MX 9301435 A1	01-10-1993
			NO 943461 A	16-09-1994
			NZ 247168 A	28-03-1995
			WO 9318757 A1	30-09-1993
			US 5529789 A	25-06-1996
			ZA 9301858 A	16-09-1994